REMARKS

Claims 1-3 are pending in the instant application. Claims 1-3 have been rejected. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

I. Rejection of Claims Under 35 U.S.C. §103

Claims 1-3 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Coligan et al. (Current Protocols in Immunology, Green Publishing Associates and Wiley-Interscience, New York, 1991; pages 2.1.1-2.1.3, 2.1.9-2.1.11, and 2.1.17-2.1.22) in view of U.S. Patent 5,077,216, Zwaldo et al. (1987) (IDS Reference BA), and Zwaldo et al. (1992) (IDS Reference AX); and newly cited Hogger et al. ((1998) *Pharma. Res.* 15:296-302) as evidenced by Sulahian et al. ((Sept. 2000) *Cytokine* 12:1312-1321).

The Examiner suggests that Coligan et al. teach ELISA assays with capture and detection antibodies for use in screening biological fluids for antigen content. It is suggested that while Coligan et al. do not teach a method for detecting an early signaling event in an inflammatory response comprising detecting CD163 with antibodies directed against CD163, wherein the antibody is MAC-158 or MAC-48, the '216 patent teaches a method of detecting p155 antigen using MAC-158 and MAC-48. The Examiner further suggests that Zwaldo et al. (1987) teach that RM3/1 antigen is useful for monitoring an early signaling event in an inflammatory response in a patient because Zwaldo et al. teach that depending on the stage of inflammation RM3/1 antigen is expressed at different levels and in acute inflammation, RM3/1

antigen is expressed to varying degree depending on the stage of inflammation. The Examiner suggests that it would be immediately obvious to one of skill in the art that Zwaldo et al. teach that detection of the expression of RM3/1, *i.e.*, CD163 is useful for monitoring an early signaling event in an inflammatory response. It is suggested that Sulahian et al., based on the teaching of Zwaldo et al., suggest that CD163 bright macrophages play a role in the resolution of inflammation. Further, it is suggested that Hogger et al. teach that injection of glucocorticoids into primates or human volunteers results in an increase in RM3/1 positive blood monocytes within 6 hours and monocytes expressing RM3/1 antigen are present in acute inflammation. The Examiner suggests that based on the teachings of the cited reference, the present invention is obvious. Applicants respectfully traverse this rejection.

Applicants respectfully disagree with the Examiner's analysis of the cited references. Coligan et al. teach a general method of ELISA, and as acknowledged by the Examiner, are silent to CD163 expression being indicative of an early signaling event in an inflammatory response cascade in the patient.

Similarly, the '216 patent is silent to CD163 expression levels in an inflammatory response. However, in any event, the '216 patent is not a valid prior art reference because at the time of filing of the present application, the inventors of the instant application and Patent No. 5,077,216 had a common obligation to assign to the Trustees of Dartmouth College (see the face of Patent No. 5,077,216).

Moreover, Sulahian et al. is not a valid prior art reference as it was published in September 2000, six months after the

effective filing date of the present application, *i.e.*, March 28, 2000.

In a proper analysis of the combined teachings of Zwaldo et al. (1987), Zwaldo et al. (1992), and Hogger et al. (1998), one of skill in the art would not reasonably find obvious the present invention as the overall teachings of the cited references is that CD163 antigen (*i.e.*, RM3/1) is associated with the down-regulatory or healing phase of the inflammatory process and NOT in an early signaling event in the inflammatory response cascade in a patient. Therefore, there would be no motivation to modify these teachings to determine whether there is a detectable elevation in the level of CD163 within 1 to 12 hours of exposure to the inflammatory stimulus indicative of an early signaling event in the inflammatory response cascade in a patient.

Specifically, Zwaldo et al. (1987) teach that "macrophages are heterogeneous in normal and inflammatory tissues and the inflammatory reactions are a very dynamic process with respect to the appearance and disappearance of various macrophage phenotypes. Here we describe a monoclonal antibody directed against a subset of monocyte/macrophages which appear in the later stage of an inflammatory reaction", namely RM3/1 monocyte/macrophages. See page 296, column 1, last two sentences of the first paragraph. Zwaldo et al. (1992) and Hogger et al. cite the findings of Zwaldo et al. (1997), respectively stating that macrophage RM3/1 is "a subtype found to be associated with the down-regulatory phase of the immune response" (see page 178, column 1, lines 2-4 of first paragraph) and "RM3/1 monocytes/macrophages appeared preferentially in the late inflammatory phase" (see page 296, column 2, fourth full

paragraph). Accordingly, as persons of skill in the art, Zwaldo et al. (1992) and Hogger et al. did not take from the teachings of Zwaldo et al. an appreciation that elevated expression of CD163 antigen is indicative of an early signaling event in the inflammatory response cascade in a patient, *i.e.*, 1 to 12 hours after exposure to the inflammatory stimulus.

Moreover, Zwaldo et al. (1992) and Hogger et al. substantiate the findings of Zwaldo et al. (1987) by showing that glucocorticoids, *i.e.*, anti-inflammatory agents generally administered to combat an inflammatory response, increase expression of RM3/1 antigen thereby facilitating healing. More to the point, Hogger et al. teach that in contrast to anti-inflammatory agents, RM3/1 expression is reduced or unchanged in response to an inflammatory stimulus. Hogger et al. indicate that "The influence of inflammatory activators - compared to the influence of the anti-inflammatory glucocorticoids - on RM3/1 antigen expression was determined by incubation of PMA and LPS with monocytes. After PMA treatment the number of positive cells was statistically significantly reduced (paired t-test, $p \leq 0.05$) whereas LPS had no effect on RM3/1 expression compared to the nontreated control cells." This is in contrast to the teachings of the present invention, which demonstrate that CD163 is one of the earliest markers of an acute inflammatory response that can be detected in plasma (see page 11, lines 12-15 of the present application) as CD163 levels increase at 60 minutes following cardiopulmonary bypass and return to slightly below baseline levels on post-operative day 1 (see page 10, lines 8-11) and CD163 levels peak at 1 to 2 hours and remain elevated at 12 hours

compared to baseline levels in healthy volunteers given LPS infusions (see page 10, lines 30-35).

Accordingly, while Zwaldo et al. (1987) teach and correlate RM3/1 antigen levels in the later stages of an acute inflammatory condition (*i.e.*, 2 days up 19 days of experimental gingivitis, see Figure 3 at page 301), and Zwaldo et al. (1992) and Hogger et al. teach and correlate RM3/1 antigen levels in response to anti-inflammatory stimuli, there is no teaching, suggestion or motivation to modify the teachings of Coligan et al. to measure the levels of CD163 within 1 to 12 hours of exposure to an inflammatory stimulus for detecting an early signaling event in an inflammatory response cascade in a patient. Thus, these references fail to establish a *prima facie* case of obviousness as required by MPEP 2143. It is therefore respectfully requested that this rejection be withdrawn.

II. Rejection of Claims Under 35 U.S.C. §112

Claims 1-3 have been rejected under 35 U.S.C. 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner suggests that "determining whether there is a detectable elevation in the level of CD163 within 1 to 12 hours of exposure to the inflammatory stimulus indicative of an early signaling event" represents a departure from the specification and claims as originally filed. It is suggested that the specification and claims as originally filed only support "demonstrating that elevation in the level of CD163 within 1 to

12 hours acts as an early signaling event in the inflammatory response". Applicants disagree with this rejection

As originally filed, claim 1 was drawn a method for detecting the presence of CD163 in a biological sample comprising contacting the sample with a CD163 capture antibody to form a CD163-antibody complex; and contacting the CD163-antibody complex with a CD163 detection antibody so that the levels of CD163 in the sample are detected. As amended, the claims now clarify the nature of the biological sample (*i.e.*, from a patient known to have or suspected of having been exposed to an inflammatory stimulus) and the significance of elevated levels of CD163 in the sample (*i.e.*, an elevation in the level of CD163 within 1 to 12 hours of exposure to the inflammatory stimulus is indicative of an early signaling event in the inflammatory response) as demonstrated by the experiments performed by Applicants. In these experiments, "Plasma samples were taken at baseline (before administration of LPS), and then at various time points after LPS infusion up to 72 hours after infusion initiation. Levels of CD163 in plasma were measured using the assay of the present invention. Soluble CD163 levels in plasma increased as much as 7-fold compared to baseline levels, peaked at 1 to 2 hours, and remained elevated in 4 of 5 volunteers at 12 hours post LPS administration... Theses data demonstrated that soluble CD163 is one of the earliest changes induced by an acute inflammatory response that can be detected in plasma. Therefore, CD163 acts as an early signaling event in the inflammatory response cascade." In this regard, Applicants disclose, contacting a biological sample obtained from a patient known to have or suspected of having been exposed to an inflammatory stimulus with a CD163

capture antibody to form a CD163-antibody complex; contacting the CD163-antibody complex with a CD163 detection antibody; detecting CD163 levels in the biological sample; and determining whether there is a detectable elevation in the level of CD163 within 1 to 12 hours of exposure to the inflammatory stimulus indicative of an early signaling event in the inflammatory response cascade in the patient. Accordingly, the method steps are not a departure from the teachings of the instant specification as each step is taught and exemplified in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. It is therefore respectfully requested that this rejection under 35 U.S.C. 112, first paragraph, be reconsidered and withdrawn.

III. Conclusion

The Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

Jane Massey Licata
Registration No. 32,257

Date: **January 18, 2006**

Licata & Tyrrell P.C.
66 E. Main Street
Marlton, New Jersey 08053
(856) 810-1515